Ecological and evolutionary challenges for wildlife vaccination

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ABSTRACT

Wildlife vaccination is of urgent interest to reduce disease-induced extinction and zoonotic spillover events. However, several challenges complicate its application to wildlife. For example, vaccines rarely provide perfect immunity. While some protection may seem better than none, imperfect vaccination can present epidemiological, ecological, and evolutionary challenges. While anti-infection and anti-transmission vaccines reduce parasite transmission, anti-disease vaccines may undermine herd immunity, select for increased virulence, or promote spillover. These imperfections interact with ecological and logistical constraints that are magnified in wildlife, such as poor control and substantial trait variation within and among species. Ultimately, we recommend approaches such as trait-based vaccination, modeling tools, and methods to assess community- and ecosystem-level vaccine safety to address these concerns and bolster wildlife vaccination campaigns.

The potential of wildlife vaccines

Vaccination, the process of exposing the immune system to an antigen to induce pathogen resistance, is a powerful tool for controlling disease. The benefits of vaccination are twofold: recipients are directly protected against infection and unvaccinated hosts are indirectly protected through **herd immunity** (**Glossary**), which reduces transmission and parasite-mediated harm to host populations [1]. Vaccination has been vastly successful for humans and livestock [2,3]. Successful vaccination campaigns against rabies in raccoons (*Procyon lotor*), red foxes (*Vulpes vulpes*), gray foxes (*Urocyon cinereoargenteus*), and coyotes (*Canis latrans*) suggest that vaccination efforts could be directed towards emerging infectious diseases (EIDs) that cause devastating host declines, e.g., amphibian chytridiomycosis, white nose syndrome, Tasmanian devil facial-tumor disease, and Ebola [4–10]. The success of vaccination in human and livestock populations, the pressing need for disease control tools in wildlife conservation, and the ever-increasing threat of zoonotic **spillover** events support a clear need to develop vaccination as an intervention tool for wildlife disease control. However, several outstanding challenges and questions remain before vaccination can emerge as a reliable tool for wildlife disease control. We argue that accounting for the limitations of imperfect vaccines, host and non-host ecology, and individual physiology in the development of vaccination campaigns is vital for harnessing the potential of wildlife vaccines successfully.

Objectives of wildlife vaccination

Biodiversity conservation and the prevention of pathogen spillover are two urgent concerns of wildlife disease control. Emerging diseases of wildlife threaten population

and species persistence and contribute significantly to the ongoing loss of biodiversity [11]. Additionally, wildlife populations are **reservoir hosts** for many **zoonotic pathogens** such as rabies, Nipah virus, and coronaviruses that threaten the health of humans [12].

Controlling disease in wildlife reservoir populations can reduce spillover transmission, but complete prevention of spillover risk from a known pathogen requires elimination or eradication of a parasite within a reservoir host to prevent zoonotic transmission. Vaccines may be able to achieve this objective, but given the inherent antigenic specificity of all known vaccines, they will not prevent novel pathogen emergence. Theory underlying eradication often identifies a critical level of vaccine coverage, which drives the **effective reproductive ratio (R_{eff})** of a pathogen below the threshold value of one [1]. Combating rinderpest virus reintroduction during the eradication campaign exemplifies the intense effort needed for eradication [3].

In contrast, vaccination for conservation aims to maximize the persistence of host populations and communities by decreasing the risk of disease-induced extinction, rather than through achieving parasite elimination. Wildlife populations can generally withstand small-scale disease outbreaks, and so conservation-motivated vaccination does not always require pathogen eradication [13]. Thus, vaccination coverage required for conservation-motivated disease control tends to be lower than that required for spillover prevention. For example, modeling estimates suggest that maintaining low vaccination coverage, between 20-40%, will stave off rabies-induced extinction of Ethiopian wolves (*Canis simensis*)[13].

Vaccine efficacy and modes of imperfection

Despite their potential for controlling wildlife disease, vaccines rarely provide perfect immunity, which can compromise herd immunity or contribute to the evolution of increased **parasite virulence** [14]. For example, a prototype vaccine partially protects amphibians from *Batrachochytrium dendrobatidis*; vaccination decreases, but does not eliminate, parasite proliferation [15]. In contrast, a theoretically perfect vaccine would provide permanent and complete resistance to infection for all recipients, but vaccines considered for wildlife often fall short of this definition [14]. Three broad aspects of vaccine imperfection are often discussed in the literature: waning, leaky, and partial immunity. However, "leaky" immunity is used inconsistently and imprecisely, generating confusion. One reason for this is that modeling frameworks, such as *Susceptible-Infected-Resistant* (SIR) compartment models can make it difficult to incorporate some types of vaccine imperfections. Therefore, we suggest a clarified categorization based on **waning**, **binary** and **partial immunity.** Importantly, these categories are not mutually exclusive, and we discuss the impacts of these varying levels of immunity on wildlife populations, vaccine efficacy, modeling frameworks.

Waning immunity

Waning describes the loss of resistance to infection over time. Individuals can vary in their waning rate, and immunity can be restored by subsequent exposures, i.e., "boosters". Vaccine-induced immunity often wanes faster than immunity generated from natural infection, which can leave vaccinated individuals at higher risk during recurrent or cyclical epidemics [16]. For example, Eastern Equine Encephalitis virus vaccination in

92 sandhill (*Grus americana*) and whooping cranes (*Grus canadensis*) waned rapidly,
93 requiring booster vaccination within 30 days [17]. Life history traits, immune boosting
94 sources, and waning rate interact to determine vaccine utility [18]. Waning immunity is
95 routinely and relatively easily incorporated into SIR compartment models by allowing
96 resistant individuals to reenter the susceptible class.
97
98 *Binary immunity*
99 Binary immunity occurs when vaccination does not induce immunity in all
100 recipients [19]. This generates a binary outcome, wherein hosts are either resistant or
101 susceptible, with no intermediate outcome. Binary outcomes of immunization have also
102 been described as an "all-or-nothing qualitative response" [20]. For example, high rates
103 of binary vaccine outcomes for the varicella vaccine in humans prompted the
104 recommendation for a second dose within months of the first [21]. Differences in vaccine
105 **immunogenicity**, **adjuvants,** vaccine storage, dosage, administration, host infection
106 status, competence of the host's immune system, and host genetics can all shape binary
107 immunity [19,22]. Random binary immunization outcomes are often incorporated into
108 SIR models by effectively lowering vaccination coverage by the proportion of binary
109 failure [23]. However, if certain host types are more prone to vaccine failure, then it
110 might be critical to address how these different failure rates among different host class
111 affect disease dynamics [24].
112
113 *Partial immunity*

In contrast to binary efficacy, which assumes a vaccine either succeeds in inducing an acquired immune response or fails, vaccines that provide partial immunity may not completely prevent infection, disease symptoms, or transmission in an immunized host. Partial immunity allows for vaccine efficacy to be measured on a proportional gradient from 0-1, rather than as a qualitative all-or-nothing response [25,26]. One critical complication is that partial immunity may impact a number of infection outcomes, such as resistance to infection, disease attributed to infection, and infectiousness [27]. The functional consequences of these changes are detailed below. Partial immunity is less easily incorporated into SIR-type models and has therefore been relatively neglected compared to other modes of imperfection. Individual-based models (IBMs), which explicitly track individual traits and histories may be much better suited to investigate this vaccine imperfection.

Functional mechanisms and consequences of imperfect vaccines

Different resistance responses to imperfect vaccines have unique ecological and evolutionary consequences. Imperfect immunization can confer the following three phenotypic types of resistance responses: 1) anti-disease, 2) anti-infection, and 3) anti-transmission (**Figure 1**). These are also not mutually exclusive, and they can be assessed using either binary (qualitative) or partial (quantitative) metrics [26,28,29]. Because the majority of vaccines are imperfect, anticipating and addressing their potential deleterious consequences is a priority in determining vaccination feasibility in a wildlife context. For example, the **imperfect-vaccine hypothesis** postulates that partial immunity upon vaccination could drive the evolution of increased pathogen virulence, and the risk of

vaccine-driven virulence evolution is dependent on the vaccination phenotype and efficacy [29].

Anti-disease vaccines

Anti-disease vaccines reduce virulence (i.e., increase **host tolerance**) without necessarily reducing the risk of infection or subsequent transmission. Therefore, these vaccines directly benefit recipients, but can counteract herd immunity if the infectious period is lengthened. Studies on Marek's disease in poultry and helminth and tuberculosis **coinfections** in African buffalo show that interventions which reduce the mortality of infected hosts, without decreasing infection or transmission rates, increase parasite transmission in populations by extending the infectious period [29,30]. Despite this potential for increased transmission, anti-disease vaccines may still be effective for conservation if their net effect reduces total parasite-induced mortality or reproductive costs. A prototype anti-*Chlamydia pecorum* vaccine for koala (*Phascolarctos cinereus*) conservation offers potential as a therapeutic vaccine as it reduces disease in unexposed and infected koalas, with some reduction in infection incidence and loads [31]. However, anti-disease vaccines are unlikely to reduce spillover risk, precisely because they can promote transmission.

Evolutionarily, lengthening the infectious period through anti-disease vaccination is theorized to relax selection against high virulence [27,29]. This prediction, derived from the **transmission-virulence trade-off hypothesis**, arises because limiting host death allows for otherwise highly virulent genotypes to persist and even be favored by selection [29]. While experimental evidence explicitly demonstrating increased virulence

160 driven by vaccination is lacking, a recent study on house finches (*Haemorhous*
161 *mexicanus*) parasitized by the bacteria *Mycoplasma gallisepticum* demonstrated that an
162 anti-disease phenotype conferred by a natural primary infection facilitated a two-fold
163 increase in the fitness advantage of a high virulence strain during secondary infections
164 [32]. However, anti-disease vaccines that vary in degree of protection among immunized
165 individuals may be less risky for vaccine-driven virulence evolution, as variance in host
166 protection will not uniformly favor the evolution of increased parasite virulence [27].
167
168 *Anti-infection and anti-transmission vaccines*
169 Vaccines that prevent or reduce parasite establishment in an immunized host are
170 considered anti-infection vaccines. Anti-transmission vaccines, on the other hand, may
171 permit infection but prevent or reduce onward transmission from the recipient. Both
172 phenotypes contribute to herd immunity, and epidemiological models predict that parasite
173 elimination can be achieved with high rates of coverage and efficacy [28]. Thus, both
174 anti-infection and anti-transmission vaccines can be effective for spillover prevention and
175 conservation. The *Mycobacterium bovis* bacille Calmette-Guérin (BCG) vaccine, used to
176 prevent spillover of *M. bovis* into livestock, confers anti-infection resistance in Australian
177 brushtail possums (*Trichosurus vulpecula*), and the transmission-reducing prototype
178 *Batrachochytrium dendrobatidis* vaccine offers promise for use in amphibian
179 conservation [15,33].
180 The evolutionary consequences of these vaccines depend crucially on the mode of
181 imperfection. Binary anti-infection or anti-transmission vaccines do not favor virulence
182 evolution and can, at times, even reduce selection for parasite virulence, by preventing

183 coinfections for example [28,34]. Conversely, partial anti-infection or anti-transmission
184 vaccines can select for increased virulence [25]. Partial anti-infection and anti-
185 transmission phenotypes effectively increase the exposure dose required for
186 establishment (i.e. infectious dose), which can select for increases in parasite
187 reproduction rate [25,28]. Theory suggests that this type of anti-infection resistance
188 favors virulence evolution by encouraging the increase in intrinsic parasite reproduction
189 for successful infection establishment [25].
190
191 **Ecological and logistical challenges of vaccination exacerbated in wildlife**
192 Vaccines have strong potential to achieve disease control in wildlife. However,
193 imperfect vaccines must also overcome physiological, behavioral, and ecological factors
194 to succeed. Thus, complications arise from two primary factors: vaccine imperfections
195 and vaccine administration. Lack of control and intraspecific, interspecific, and
196 environmental heterogeneity are central sources of uncertainty in vaccine delivery,
197 uptake, and response (**Box 1**). Vaccination success hinges on high coverage of doses that
198 induce a durable immune response without harming recipients [1]. In complex ecological
199 communities, indirect deployment (i.e., oral baiting) campaigns risk simultaneously over-
200 and under-dosing many organisms because wildlife can vary in 1) the amount of
201 inoculum consumed or encountered and 2) their physiological response to a given dose.
202 Heterogeneity in host behavior, morphology, and habitat use all influence
203 infection risk, and probability of vaccine exposure [35–37]. Assessing vaccine exposure
204 in target and non-target wildlife can be done using biomarkers, such as fluorescent
205 Rhodamine b [38]. Moreover, the immunological traits of most wildlife hosts remain

poorly known, and even closely related species can exhibit marked variation in response to vaccination [39]. In vaccination campaigns using indirect deployment, assessing vaccine safety and impact on non-target hosts and non-hosts is a critical step to anticipating and preventing harmful unintended consequences on ecological communities and ecosystem functioning. **Dose-response profiles** are a useful and routine tool for assessing consequences of over- and under-dosing wildlife. Specifically, dose-response profiles can be useful for quantifying differences in dose-specific immune responses for distinct classes of hosts (e.g., species identity, developmental stage, age class, genotype). Additionally, the effect of vaccination on non-target wildlife can be evaluated by tracking community diversity metrics (e.g. abundance, richness, and evenness) and ecosystem function pre- and post-administration in both placebo and vaccinated environments [38]. Furthermore, **trait-based vaccination** may help to overcome issues related to patchy coverage and dosing.

Trait-based vaccination

Which hosts should be prioritized for vaccination? Host factors such as age, immunity, behavior, and genetics all influence **host competence** [40]. These heterogeneous factors contribute significantly to disparities in parasite susceptibility and transmission between hosts, leading to relatively few individuals being responsible for most parasite transmission in a population [41]. This observation can be harnessed to tailor control methods using trait-based vaccination.

Random mixing is a fundamental assumption of classic vaccination and transmission models, but network analyses of wildlife show that traits such as

territoriality or sociality often reveal non-random contacts, elevating the importance of accounting for contact and home range heterogeneity in vaccination [42,43]. Targeted vaccination of **superspreaders** has been continually proposed as a method to reduce required immunization coverage [44,45]. For example, targeted vaccination of socially-central chimpanzees, determined by detailed behavioral data or approximated using trait-based estimates, can significantly reduce the vaccination coverage threshold [44]. Incorporating contact networks into **transmissible vaccine** models, using an individual-based approach, could assess if behaviors associated with superspreading, such as gregariousness or boldness, increase vaccine transmission [46,47]. Alternatively, vaccination for conservation could target individuals that are disproportionately important to population growth or persistence [48].

Modeling wildlife vaccination

Susceptible-Infected-Resistant (SIR) models are the most common models used for predicting vaccination outcomes [27]. While valuable for modeling waning and binary modes of imperfection, SIR models cannot capture the complexities of partial immunity, especially when spatial dynamics, social interactions or individual history are important [23,27,49]. Limitations of modeling partial immunity using ordinary differential equations (ODEs) can be overcome using individual-based models (IBMs), which are able to incorporate different host immune responses and space-based behaviors such as territoriality and migration [49]. For example, in the case of fox rabies control in Europe, IBM predictions recommended the use of a lower coverage vaccination strategy relative to an SIR model [50]. This lower coverage strategy was carried out successfully

and saved considerable resources [49].While the simplicity and analytical tractability of ODE models can offer considerable advantages, we advocate for the increased consideration of IBMs in the study of wildlife disease because they can represent individual-level physiology, connect seamlessly with transmission networks or spatially-explicit movement models, and accommodate individual history and heterogeneity [49].

Concluding Remarks

Vaccines can advance biodiversity conservation and spillover control. However, vaccine imperfections can substantially compromise the achievement of herd immunity or promote the evolution of increased virulence, yet they are not always accounted for in theory, planning, or analysis of vaccine use in wildlife. Wildlife vaccination offers a frontier to explore advancing questions in eco-immunology, imperfect immunity, and disease control innovation. The biological factors shaping vaccination success, feasibility, and efficacy should be as central to decisions regarding wildlife vaccination as logistical limitations and financial resources (**Outstanding Questions**). Thorough empirical assessment of the vaccine-host-parasite biology can both 1) prevent impractical vaccination campaigns and 2) ameliorate challenges regarding vaccine dose and coverage, saving time and limiting adverse outcomes.

Disentangling potential modes of imperfection is critical for predicting outcomes of vaccination. Incorporating these effects into models and experiments can predict otherwise counterintuitive deleterious outcomes, such as increased transmission caused by anti-disease resistance. We suggest that IBMs should be selected for vaccines conferring partial immunity or systems in which space-based behaviors drive disease

dynamics. Additionally, vaccination outcomes should be simultaneously studied across ecological scales and evolutionary time. Imperfect vaccines impose subtle tension between individual- and population-level benefits, and deeper theoretical examination can help prevent the implementation of unfeasible or potentially harmful vaccines.

Furthermore, wild hosts and parasites are inherently heterogeneous and poorly controlled. Dose-response profiles and community diversity metrics should be used to account for heterogeneity when calculating safe and effective vaccine doses for wildlife individuals, populations, communities, and ecosystems. Trait-based vaccination approaches could prioritize hosts that disproportionately contribute to population persistence or parasite transmission thus minimizing coverage required for parasite eradication or host population viability. Ecological complexities and evolutionary consequences of imperfect immunity provide an abundance of challenges when vaccinating wildlife; but pursuing wildlife vaccination for use in conservation or spillover prevention is by no means foolish if informed by the system's underlying physiology and ecology.

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Glossary

Herd immunity: indirect protection of susceptible hosts by resistant hosts.

Spillover: transmission of parasites from a non-human host species to humans.

Reservoir host: a population of organisms that serve as an infection source for another host population.

Zoonotic pathogens: a parasite able to be transmitted from non-human animals to humans.

Effective reproductive ratio (R_{eff}): the number of secondary infections a primary infection contributes in a population with resistant individuals.

Parasite virulence: host death or pathology induced by infection.

Resistance phenotype: categories of incomplete immunity, including anti-disease immunity, anti-infection immunity, and anti-transmission immunity.

Immunogenicity: a vaccine's ability to induce an acquired immune response.

Adjuvants: vaccine additives to increase its immunogenicity.

Imperfect-vaccine hypothesis: theory suggesting that, depending on the phenotype of resistance, partial vaccination may select for increased parasite virulence.

Host tolerance: decreased mortality or pathology in response to infection.

Transmission-virulence trade-off hypothesis: hypothesis derived from the assumption that transmission rate and virulence are correlated, predicting that an intermediate level of virulence is favored by selection.

Coinfections: two or more parasite species simultaneously infecting the same host**.**

Dose-response profiles: quantifying an organism's physiological response to varying doses of vaccine.

Trait-based vaccination: vaccine distribution prioritizing individuals with specific characteristics.

Host competence: the relative ability of a host to become infected by and transmit a parasite.

Superspreader: an individual that disproportionately contributes to parasite transmission within a given population.

Transmissible vaccine: vaccines that autonomously spread from treated to untreated individuals.

Enzootic: a pathogen endemic in non-human animals.

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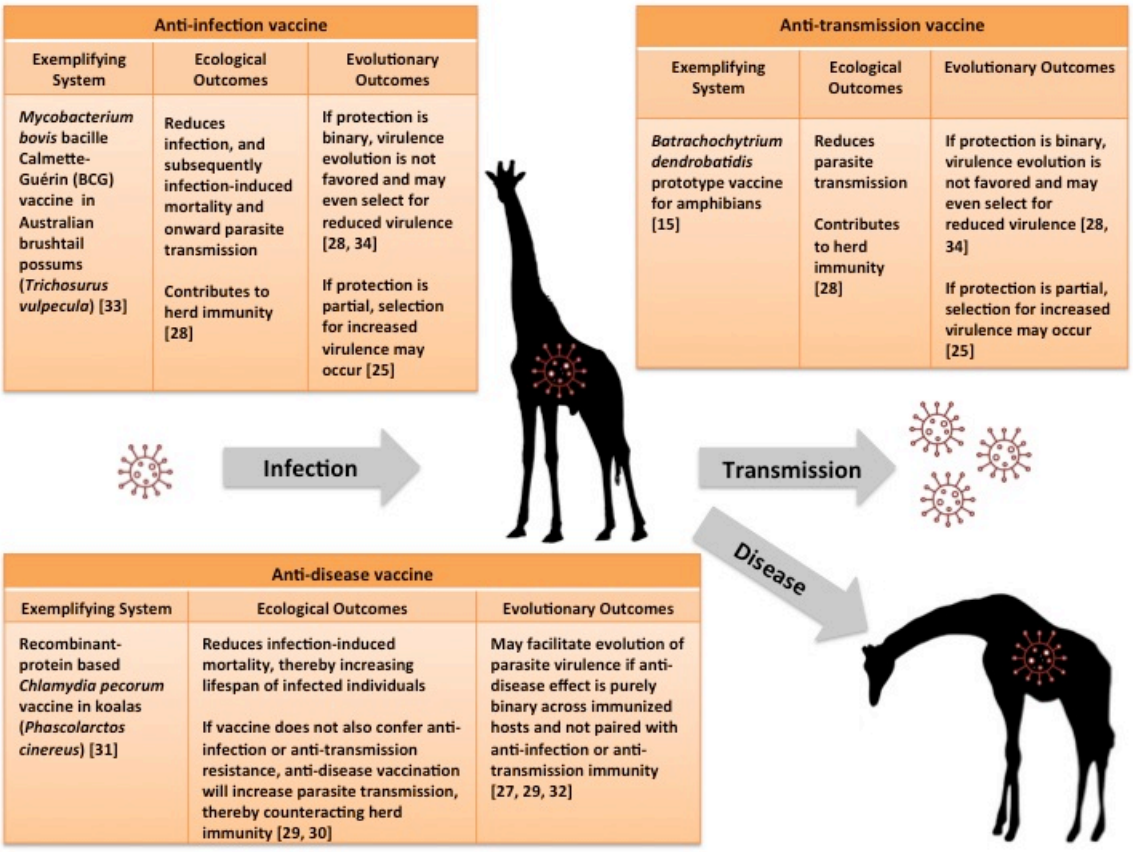

Figure 1. Imperfect vaccines can be categorized by the phenotypic resistance effects on vaccinated hosts, such as anti-infection, anti-disease, and anti-transmission. Each of these non-exclusive categories can influence epidemiology and pathogen evolution.

Box 1. Canid rabies vaccination campaigns: limitations to control

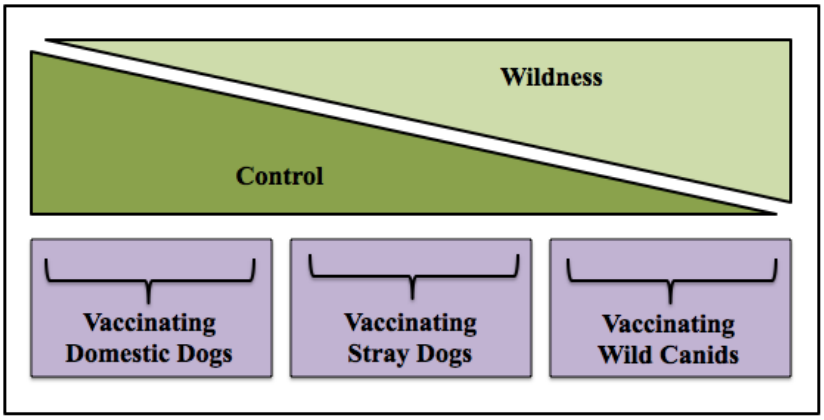

Figure 2. Rabies vaccination on a gradient of wildness.

Rabies vaccination of canids has been used to both prevent spillover transmission into human populations and protect endangered wildlife [51]. Rabies vaccination of domestic dogs, stray dogs, and wild canids demonstrates vaccination across a gradient of control and wildness (**Figure 2**). Globally, domestic dogs are the main source of rabies transmission to humans [52]. Consequently, owned dog vaccination is used to interrupt dog-to-human transmission and, largely due to the control afforded by ownership, has been successful in eliminating **enzootic** canine rabies in the U.S [53]. However, the unconstrained movement of stray dogs allows contact with wildlife, owned dogs, and humans, amplifying their importance in rabies transmission [54]. Difficulty catching stray dogs contributed to poor coverage, and hence failure, in a mass rabies vaccination campaign in Bangkok, Thailand [55]. Furthermore, high population growth, turnover, and translocation rates of stray dogs intensifies the challenge of achieving and maintaining vaccination coverage sufficient for herd immunity [54–56]. Combining vaccination with neutering can combat these challenges [57].

Vaccination of wildlife against rabies to prevent spillover into humans and domestic animals have also been hugely successful campaigns; locally eliminating rabies in red foxes and coyotes, while decreasing its prevalence in gray foxes [4–6]. This success is undoubtedly driven by the advent of oral bait vaccines, which can be distributed across large geographic scale [6]. Yet, although oral vaccination reduces the need for wildlife control via capture and handling and increases the geographic scale of administration, successful oral vaccination requires ecological knowledge of target and non-target foraging behaviors and home ranges for baiting, population turnover rates for estimating length of vaccination protection, and species-specific immunological responses [6,58,59]. Rabies vaccination has also been implemented as a conservation measure for endangered wild canids, such as the Ethiopian wolf (*Canis simensis*) and African wild dogs (*Lycaon pictus*) [56,60].

In these canid vaccination campaigns, control at the individual level, such as compliance, handling, and capture, prove most challenging. Thus, strategies that prioritize population-level measures, i.e., economic incentives through government support for owned dog vaccination, managing stray dog populations through neutering, and oral baiting of free-roaming and wild canids, significantly enhance vaccination success.